Remarks

In accordance with the present invention, there are provided methods for testing a compound for its ability to regulate transcription-activating effects of a peroxisome proliferator activated receptor-gamma (PPAR-γ). Invention methods comprise assaying for changes in the level of reporter protein present as a result of contacting cells containing PPAR-γ (either endogenous to the host cell or introduced recombinantly) and a reporter vector with the test compound of interest. Compounds identified employing invention methods are useful in the treatment of pathological conditions such as diabetes.

Claims 16, 18-20 and 27-45 were pending before this communication. By this communication, claims 27, 28, 36, 44 and 45 have been amended to define Applicants' invention with greater particularity. These amendments add no new matter and are fully supported by the specification and the original claims.

Accordingly, claims 16, 18-20 and 27-45 remain currently pending. The present status of all claims in the application, and current amendments thereto, are provided in the listing of claims presented herein beginning on page 2.

The rejection of claim 27 under 35 U.S.C. § 102(b), as allegedly being anticipated by Marcus *et al., Proc. Natl. Acad. Sci.* 90:5723-5727, 1993 (hereinafter referred to as "Marcus"), is respectfully traversed. Applicants' invention, as defined by claim 27, is clearly distinguishable over Marcus by requiring contacting the test cells with at least two compounds. Claim 27 requires contacting the cells with (i) a test compound and (ii) at least one additional compound that is a PPAR-γ agonist. Applicants respectfully submit that the language of the claim makes it clear that two exogenous compounds were contemplated because the second must be a known PPAR-γ agonist. Thus, the Examiner's assertions that Marcus teaches that COS cells may contain endogenous activators of PPAR is inapplicable. Marcus simply does not teach or suggest contacting PPAR-γ-containing cells with at least two compounds as a method of evaluating a test compound for its ability to regulate transcription-activating effects of PPAR-γ.

However, in order to advance prosecution and reduce the issues, Applicants have amended claim 27 to further clarify that the cells are contacted with (i) a test compound, and (ii) at least one additional compound that is a PPAR-γ agonist.

Accordingly Applicants respectfully request reconsideration and withdrawal of this rejection of claim 27 under 35 U.S.C. § 102(b).

The rejection of claims 36, 37 and 39-42 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Webster *et al.*, *Cell* 54:199-207, 1988 (hereinafter referred to as "Webster") in view of U.S. Patent 6,200,802 to Greene *et al.* (hereinafter referred to as "Greene"), is respectfully traversed. Applicants' invention, as defined by claim 36, is directed to a method of testing a compound for its ability to regulate PPAR-γ. In contrast and as previously presented (see Response, Paper No. 31, faxed May 27, 2003), Webster merely uses known receptor activators in a mechanistic study to localize the activation domains of the human estrogen or glucocorticoid receptors. Webster clearly does not teach or suggest the use of GAL4-PPAR-γ chimeras to test compounds for PPAR-γ regulation.

Moreover, Greene is unable to cure the deficiencies of the primary reference Webster, because it also does not teach or suggest the use of GAL4-PPAR-γ chimeras to test compounds for PPAR-γ regulation. Greene merely relates to the identification of PPAR-γ receptors.

Also as previously presented, Webster uses known activators to study receptor activation because the goal of Webster is to localize functional activation domains. The presence of an unknown or test compound would be completely antithetical to the desired goal because a change in activation could no longer be attributed solely to the receptor domains being studied to localize the activation domain. Furthermore, Greene does not even mention the use of any bioassay as claimed herein.

In contrast, the present invention focuses on identifying novel PPAR-γ modulators, *i.e.*, testing compounds for their ability to modulate PPAR-γ. Only Applicants have used chimeric GAL4-PPAR-γ receptors in the identification of novel compounds capable of regulating PPAR-γ

from a pool of uncharacterized test compounds in an assay format amenable to high-throughput screening.

However, in efforts to advance prosecution and reduce the issues, and in response to the Examiner's assertion that "the feature upon which Applicant relies (i.e., contacting cells with an unknown compound), is not recited in the claims" (see Office Action, Paper No. 32, at page 6, lines 15-17), claim 36 has been amended to clarify that the method comprises "contacting cells containing a GAL4 chimeric PPAR-γ receptor and a reporter vector with a test compound" (emphasis added).

Therefore, the invention as defined by claims 36 (and claims 37 and 39-42 dependent thereon) cannot be obvious over the combination of Webster and Greene. Accordingly, Applicants respectfully respect reconsideration and withdrawal of this rejection of claims 36, 37 and 39-42 under 35 U.S.C. § 103(a).

The rejection of claim 28 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Ikonen *et al., Endocrinology* **135**:1359-1366, 1994 (hereinafter referred to as "Ikonen") in view of Marcus, is respectfully traversed. Applicants' invention, as defined by claim 28, distinguished over the applied art by requiring contacting cells containing PPAR-γ and a reporter vector with (i) a test compound, and (ii) a PPAR-γ antagonist. Ikonen is merely a study of the effect of known modulators of protein phosphorylation on the transcriptional activity of the androgen receptor. Thus, Ikonen does not teach or suggest a receptor expression vector comprising a DNA segment encoding PPAR-γ (as acknowledged by the Examiner, see Office Action, Paper No. 32, at page 7, lines 12-13); nor does Ikonen teach or suggest contacting cells containing a PPAR-γ expression vector with at least two compounds including a PPAR-γ antagonist.

Marcus is unable to cure the deficiencies of the primary reference because as discussed above, Marcus does not teach or suggest contacting cells with a test compound and a second compound of any kind. Furthermore, neither reference provides the motivation to combine the two references to arrive at a method of evaluating test compounds for their ability to modulate PPAR-γ activity in the presence of a PPAR-γ antagonist as claimed herein. The combination of

these references without the motivation to do so is improper hindsight reconstruction in light of Applicants' present disclosure.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of claim 28 under 35 U.S.C. § 103(a).

The rejection of claims 44 and 45 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Webster in view of Greene and Ikonen, is respectfully traversed. As discussed above, Webster does not teach or suggest the use of GAL4-PPAR-γ chimeras to evaluate test compounds for PPAR-γ regulation. Greene is unable to cure the deficiencies of the primary reference, because it also does not teach or suggest the use of GAL4-PPAR-γ chimeras to test compounds for PPAR-γ regulation. Greene merely discloses the identification of PPAR-γ receptors. Furthermore, Ikonen is similarly unable to cure the deficiencies of the primary reference, because it also does not teach or suggest the use of GAL4-PPAR-γ chimeras to test compounds for PPAR-γ regulation. The only connection between the three references is that they involve various ligand-activated receptors. There is no motivation, absent Applicants' disclosure, to combine the three references in efforts to arrive at Applicants' invention methods.

Accordingly, Applicants respectfully respect reconsideration and withdrawal of this rejection of claims 44 and 45 under 35 U.S.C. § 103(a).

Conclusion

In view of the above remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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